

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202292Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Management Review for Crofelemer**

Date:	August 27, 2012; <i>Revised August 30, 2012</i>
Reviewer(s):	Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Division of Risk Management (DRISK)
Team Leader	Kendra Worthy, Pharm. D., DRISK
Division Director	Claudia Manzo, Pharm., D., DRISK
Drug Name(s):	BRAND NAME is pending (crofelemer)
Therapeutic Class:	Anti-Diarrheal Agent
Dosage and Route:	Oral Tablet, 125 mg, two times a day (BID)
Application /Number:	NDA 202-292/Supplement 00/Sequence 00
Subject:	Risk Management Review for Crofelemer based on NDA submitted on December 5, 2011
Applicant:	Salix Pharmaceuticals, Inc. (Salix)
OSE RCM #:	2012-303
TSI #:	None

## INTRODUCTION

The Division of Gastrointestinal and Inborn Errors Products (DGIEP) requested a consult from the Division of Risk Management (DRISK) to evaluate whether or not a risk evaluation and mitigation strategy (REMS) is needed for crofelemer. Crofelemer is a new molecular entity (NME) proposed for the control and symptomatic relief of diarrhea in adult patients with Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) treated with anti-retroviral therapy (ART).<sup>1</sup> The applicant did not submit a proposed REMS in NDA 202-292 (dated December 5, 2011).<sup>2</sup>

## BACKGROUND

Crofelemer, a first-in-class, botanical formulation, is a gut-targeted, anti-secretory and anti-diarrheal agent prepared by isolation from the red latex sap of the plant *Croton lechleri* in the family, *Euphorbiaceae*. This plant species exists in the Western Amazon regions of South America.

Crofelemer is a potent inhibitor of cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis (CF) transmembrane conductance regulator (CFTR) chloride channel and calcium-activated chloride channels (CACC). The CFTR chloride channel and CACC regulate chloride and fluid secretion by intestinal epithelial cells. The to-be-marketed product is a 125 mg delayed-release tablet taken orally twice-a-day (BID).

### Chronic Diarrhea

The applicant cites that “approximately 30% to 40% of HIV positive (HIV+) patients experience episodic or chronic diarrhea which can result in weight loss and reduced quality of life. The etiology of diarrhea has significantly changed during the highly active anti-retroviral therapy (HART) era and more patients are now experiencing diarrhea as a side effect of ART in addition to HIV-induced enteropathy.”<sup>3</sup>

Diarrhea in HIV positive individuals is a serious, life-threatening medical condition for which no other product has been shown to be safe and effective. For persons with HIV/AIDS, secretory diarrhea remains an unmet medical need with HART.

The applicant defines secretory diarrhea as frequent, watery stools, incontinence, and urgency and claims that crofelemer produces an anti-secretory, anti-diarrheal effect due to the inhibition of CFTR and CACC in the gastrointestinal (GI) lumen. This inhibition blocks chloride secretion and high volume water loss in diarrhea, normalizing the flow of chloride ions and water in the GI tract. Crofelemer has a low potential for drug-drug interactions, and no clinically significant effects on drug metabolism.<sup>4</sup>

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<sup>1</sup> See NDA 202-292 Crofelemer, submitted to the FDA on December 5, 2011.

<sup>2</sup> See Consult Request from the DGIEP under IND 51818, NDA 202-292 Crofelemer.

<sup>3</sup> Siddiqui U, Bini EJ, Chandarana K, Leong J, Ramsetty S, Schiliro D, et al. Prevalence and impact of diarrhea on health-related quality of life in HIV-infected patients in the era of highly active antiretroviral therapy. *Journal of clinical gastroenterology* 2007 May, 41(5):484-490.

<sup>4</sup> See NDA 202-292/Sequence 00, Section *Crofelemer Background*, submitted December 5, 2011.

### Armamentarium of Anti-Motility Therapy

Currently, no product is approved for specific HIV-related chronic diarrhea. Existing anti-motility drugs, such as loperamide, difenoxin, tincture of opium, and octreotide are not indicated for specific use in HIV+ patients and may have harmful side effects. The approved anti-diarrheal medications (ADMs) do not address the underlying secretory mechanism of diarrhea in HIV+ patients and are contraindicated in combination with many commonly used ART such as ritonavir and saquinavir.

### **REGULATORY HISTORY**

- Fast Track Designation: On May 7, 1998, the FDA designated crofelemer for a Fast Track development program under IND 051-818, reconfirmed this designation at the End-of-Phase 2 meeting (May 3, 2004), and at the Pre-NDA meeting (January 19, 2009).
- NDA 202-292/Supplement-00 submitted to the Agency on December 5, 2011
- Priority Review: On February 3, 2012, the DGIEP granted Priority Review status at the Filing Meeting.
- Major Amendment: On April 6, 2012, the Prescription Drug User Fee Act (PDUFA) goal date (June 5, 2012) was extended to provide adequate time for review of additional Chemistry, Manufacturing, and Control (CMC) data to better characterize the identity, strength, purity, and quality of crofelemer. The PDUFA deadline was extended to September 5, 2012.
- Center Director Briefing: On August 6, 2012, Janet Woodcock expressed support for approval of crofelemer and agreed that further CMC characterization in a bioassay of the to-be-marketed commercial batches will be needed from the applicant prior to marketing, if approved. Though clinical efficacy is statistically modest, the DGIEP and Dr. Woodcock concluded that the efficacy results are clinically meaningful for control and symptomatic relief of diarrhea in HIV+/AIDS patients during on ART.

### **MATERIALS REVIEWED**

- NDA 202-292 submitted on December 5, 2011
- Proposed labeling for crofelemer last revised by the DGIEP on August 23, 2012

### **OVERVIEW OF CLINICAL PROGRAM**

The clinical development program for crofelemer in HIV+/AIDS patients with diarrhea during ART includes nine Phase 1 trials, one Phase 2 trial, and two Phase 3 trials. Key clinical trials for crofelemer efficacy and safety data are:

Trial 101 (ADVENT) – a confirmatory Phase 3 trial: Randomized (R), double-blind (BD), parallel-group, PBO-C, multi-center trial in HIV+ patients with diarrhea. ADVENT included a two-stage adaptive design that integrated dose selection and dose assessment into a single trial.

Trial 210 – a Phase 3 trial: R, DB, multi-center PBO-C, parallel group clinical trial designed to assess efficacy, safety, and pharmacokinetics (PK) of 3 doses of crofelemer in HIV+ patients with diarrhea; 6 days of inpatient treatment followed by 21 days of outpatient treatment.

Trial 209 – a Phase 2 trial: R, DB, multicenter, PBO-C, parallel-group study designed to assess efficacy and safety of crofelemer 500 mg beads in HIV+ patients with diarrhea.

See the **Appendix**, in this review, for details of each study design and the primary efficacy endpoints of each trial.

## **EFFICACY**

The primary efficacy endpoint for the ADVENT trial was the proportion of patients with a clinical response, defined as  $\leq 2$  watery bowel movements per week during at least 2 of the 4 weeks of the PBO-C phase. A significantly larger proportion of HIV+ patients in the crofelemer 125 mg BID treatment group experienced a clinical response compared with patients in PBO treatment group (17.6% versus 8%, 1-sided  $p = 0.0096$ ). Reductions from baseline to the end of the DB-phase were observed for the number of watery bowel movements/day and a daily stool consistency score in the crofelemer 125 mg BID group compared with PBO. The crofelemer treatment effect for clinical response (125 mg BID versus PBO) was similar in the subgroup analyses based on the duration of diarrhea from baseline.

## **CLINICAL EXPOSURE**

The mean exposure in the ADVENT trial, 4-week PBO-C phase, was 33 days (*all* crofelemer treated patients,  $N = 236$ ) and 32 days (PBO-C treated patients,  $N = 138$ ). In the long-term (LT) crofelemer safety population, a total of 352 patients were exposed to crofelemer: 229 patients treated with crofelemer 125 mg BID (to-be marketed dosage) and 123 patients treated with crofelemer  $> 125$  mg BID (mean values of 141 and 142 days, respectively). There were 101 patients treated with crofelemer 125 mg BID for  $\geq 6$  months and 71 patients treated with crofelemer for more than 6 months.

In long-term exposure, crofelemer exposure was  $\sim 9$ -fold longer in *all* crofelemer treatment groups (149.4 pt-yrs) compared with PBO treatment (16.6 years).

## **CLINICAL SAFETY**

The most common adverse events (AEs) observed in  $\geq 2\%$  of HIV+ patients in crofelemer 125 mg BID treatment groups (PBO-C phase, ADVENT trial) were upper respiratory tract infection, bronchitis, cough, flatulence, and increased serum bilirubin.

### ADVENT Trial

The treatment-emergent adverse events (TEAEs) occurring in  $\geq 2\%$  of patients in the crofelemer treatment group (125 mg BID) at a higher frequency than in PBO are:

- Infections and Infestations (all crofelemer 20% versus PBO 8%), the most common AEs were upper respiratory tract infection, bronchitis, urinary tract infection, nasopharyngitis and Giardiasis
- Gastrointestinal Disorders (16% versus 9%), the most common AEs were flatulence, nausea, hemorrhoids, and abdominal distension

- Investigations, the most common AEs were increased bilirubin and increased alanine aminotransferase. There were shifts in blood chemistry parameters related to hepatic function observed in the clinical trials; however, abnormal hepatic functions are frequently observed in HIV+ patients due to the high prevalence of concomitant hepatitis B and C infection, alcohol/drug abuse, and ART medication-related hepatotoxicity.

No crofelemer-treated patient had a TEAE leading to study drug discontinuation in the PBO-C phase of ADVENT. In the ADVENT trial (PBO-C phase), two crofelemer patients (< 1%) experienced SAEs (*Escherichia* sepsis and pneumonia, respectively), each in crofelemer 125 mg BID. In the PBO group, four patients (3%) experienced 5 SAEs (diffuse large B-cell lymphoma, phlebitis and pneumonia in one patient each, and acute pancreatitis and alcohol withdrawal, both in one subject). No deaths were reported in crofelemer-treated patients during the PBO-C phase (ADVENT trial).

Electrocardiogram (ECG) data did not demonstrate any signals suggesting a cardiac safety risk with crofelemer-treated patients compared with PBO (ADVENT trial).

#### HIV+ Integrated Safety Population

The TEAEs by SOC and PT in all crofelemer-treatment and PBO-treatment was qualitatively similar to the TEAEs observed in the ADVENT PBO-C phase for crofelemer versus PBO. Thirteen patients (5.7%) in the crofelemer 250 mg group, 16 patients (3.4%) in the crofelemer > 250 mg group, and 10 patients (3.6%) in the PBO group reported AEs as severe intensity. There was one death in a 62-year old male (crofelemer 125 mg BID) with history of HIV, hypertension, coronary artery disease, renal insufficiency, and chronic bronchitis secondary to a long history of smoking; death was attributed to cardiac arrest (at Week 12, ADVENT trial).

Non-fatal SAEs were reported for 11 patients (4.8%) in the crofelemer 250 mg group, 8 patients (1.7%) in crofelemer > 250 mg, and 6 patients (2.2%) in the PBO group. Of these 11 patients (two patients discussed earlier, one patient each experienced *Escherichia* sepsis and pneumonia). One patient experienced three SAEs (suicide attempt, cellulitis, and suicidal ideation). The remaining 8 SAEs cases were: suicide attempt, tracheobronchitis, appendicitis, syncope, hemorrhagic gastritis, radius fracture, viral gastroenteritis and prostate cancer. Both patients with suicide attempts had history of depression, anxiety, and other psychiatric conditions. All SAEs resolved except the prostate cancer and radial fracture.

There was not sufficient evidence to attribute causality between non-fatal SAEs in HIV+ Integrated Safety data and crofelemer.

#### Long-Term (LT) Crofelemer Safety

No new signals were observed in the LT clinical safety data.

The DGIEP Clinical Reviewers conclude that the safety profile of crofelemer is acceptable in HIV+/AIDS patients during ART.

## **DISCUSSION**

The DGIEP and the Center Director agree that the modest efficacy ( $p = 0.0096$ ) is clinically meaningful for the unmet medical need for the treatment of HIV-associated

diarrhea that does not respond to ADMs during ART. The most common adverse events observed in greater than or equal to 2% of HIV+ patients in the crofelemer 125 mg BID treatment groups were upper respiratory tract infection, bronchitis, cough, flatulence, and increased serum bilirubin. The adverse events observed with crofelemer treatment are not inconsistent with many safety risks observed in HIV+/AIDS patients during treatment with ART (ie., infections, gastrointestinal events, and elevated hepatic functions). The crofelemer clinical trials included background ART in HIV+/AIDS patients.

As cited earlier in this review, the applicant did not submit a proposed REMS. Both the DGIEP and the DRISK agree that the adverse events observed in the crofelemer clinical trials do not warrant a REMS to ensure that the benefits of crofelemer outweigh the risks.

Proposed labeling includes one subsection under WARNINGS AND PRECAUTIONS recommending that prescribers “Conduct a proper work-up to rule out infectious etiologies of diarrhea before starting crofelemer. If infectious etiologies are not considered, there is a risk that a patient with infectious etiologies will not receive appropriate therapy and their disease may worsen.” There is no BOXED WARNING or Medication Guide in the proposed labeling.

At the time of this review, the key regulatory issue for the applicant (of crofelemer) is to submit an adequate CMC bioassay to characterize this proposed botanical product. Botanical drugs are challenged to demonstrate CMC specifications comparable to those of pure chemical drugs. The Agency is concerned that the potential marketing batches of crofelemer may not have the same therapeutic effects observed in the clinical trials.<sup>5</sup> If approved, crofelemer would be the second botanical product approved by the Agency.<sup>6</sup>

## **CONCLUSION**

The DRISK concludes that a REMS is not necessary to ensure that the benefits of crofelemer outweigh the risks in HIV+/AIDS patients with chronic diarrhea, if this product is approved. The proposed labeling adequately addresses the observed safety risks of infectious etiology diarrhea, gastrointestinal events, and abnormal laboratory test results for chemistry parameters observed in the key clinical trials.

If further data or internal discussion requires that DRISK reconsider this conclusion, please send DRISK a new consult request at such time. This memo serves to close the existing consult request. Please notify the DRISK if you have any questions.

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## **APPENDIX**

### **CLINICAL TRIALS**

#### **Trial 101 (ADVENT)**

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<sup>5</sup> Cross-Discipline Team Leader Review written by Anil Raipal, M.D., Clinical Team Leader, DGIEP

<sup>6</sup> On November 9, 2006, the FDA-approved its’ first botanical drug, VEREGEN (Polyphenon® E), a special extract of green tea as a prescription drug for the topical treatment of genital warts caused by the human papilloma virus (HPV).

Confirmatory Phase 3 trial: Randomized (R), double-blind (BD), parallel-group, PBO-C in HIV+ patients with diarrhea. ADVENT included a two-stage adaptive design.

- Stage I: Determined the optimal dose of crofelemer (125 mg, 250 mg, 500 mg BID) for treatment of diarrhea in HIV+ patients.
- Stage II: Continued to assess the proportion of HIV+ patients with diarrhea who experience relief of diarrhea with a selected dose of crofelemer compared to PBO.
- Stage I + Stage II: Consisted of a 10 (+4) day single-blind, PBO-screening phase followed by randomization into a 31-day (4-week), DB, PBO-C phase and concludes with a 20-week PBO-free (PF) Extension Phase.

Primary Efficacy Endpoint: Proportion of patients with a clinical response, defined as  $\leq 2$  watery bowel movements per week during at least 2 of the 4 weeks of the PBO-C phase.

### **Trial 210**

Phase 3 trial: R, DB, multi-center PBO-C, parallel group clinical trial designed to assess efficacy, safety, and pharmacokinetics (PK) of 3 doses of crofelemer; 6 days of inpatient treatment followed by 21 days of outpatient treatment.

- Patients were randomized to 1 of 4 treatment groups at a ratio of 1:1:1:1 with approximately 80 patients/treatment group: crofelemer 500 mg Beads QID, 500 mg Tablets QID, 250 mg Tablets QID, or PBO QID.

Primary Efficacy Endpoint: Change from baseline in daily stool weight during the in-patient period (Days 1 to 7 in Trial 210; Days 1 to 4 in Trial 209).

### **Trial 209**

Phase 2 trial: R, DB, multicenter, PBO-C, parallel-group study designed to assess efficacy and safety of crofelemer 500 mg beads in HIV+ patients with diarrhea.

Primary Efficacy Endpoint: Same as in Trial 210

Note that these clinical trials did not use crofelemer dose modifications with respect to the CD-4 cell count and HIV viral load.

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/s/  
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CAROLYN L YANCEY

08/31/2012

Risk Management Review for Crofelemer (no REMS warranted based on clinical safety).

CLAUDIA B MANZO

08/31/2012

concur